

81 -- 89. A method of activating expression of an endogenous cellular gene, the method comprising the steps of:

administering to the cell a nucleic acid molecule comprising a zinc finger protein encoding-nucleic acid operably linked to a promoter, wherein the nucleic acid molecule expresses a first zinc finger protein in the cell; and

contacting a first target site in the endogenous cellular gene with the first zinc finger protein, wherein the K_d of the first zinc finger protein is less than about 25 nM;

thereby activating expression of the endogenous cellular gene to at least about 150%.

90. The method of claim 89, wherein the step of contacting further comprises contacting a second target site in the endogenous cellular gene with a second zinc finger protein, wherein the second zinc finger protein is encoded by a second zinc finger protein-encoding nucleic acid operably linked to a promoter.

91. The method of claim 90, wherein the first and second target sites are adjacent.

92. The method of claim 91, wherein the first and second zinc finger proteins are covalently linked.

93. The method of claim 89, wherein the first zinc finger protein is a fusion protein comprising a regulatory domain.

94. The method of claim 93, wherein the first zinc finger protein is a fusion protein comprising at least two regulatory domains.

95. The method of claim 90, wherein the first and second zinc finger proteins are fusion proteins, each comprising a regulatory domain.

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96. The method of claim 95, wherein the first and second zinc finger protein are fusion proteins, each comprising at least two regulatory domains.

97. A method of activating expression of an endogenous cellular gene, the method comprising the steps of:

administering to the cell a nucleic acid molecule comprising a fusion zinc finger protein-encoding nucleic acid operably linked to a promoter, wherein the nucleic acid molecule expresses a fusion zinc finger protein in the cell, and wherein the fusion zinc finger protein comprises six fingers and a regulatory domain; and

contacting a target site in the endogenous cellular gene with the fusion zinc finger protein, wherein the K_d of the fusion zinc finger protein is less than about 25 nM;

thereby activating expression of the endogenous cellular gene to at least about 150%.

98. The method of claim 89, wherein the cell is selected from the group consisting of animal cell, a plant cell, a bacterial cell, a protozoal cell, or a fungal cell.

99. The method of claim 98, wherein the cell is a mammalian cell.

100. The method of claim 99, wherein the cell is a human cell.

101. The method of claim 89, wherein expression of the endogenous cellular gene is activated to at least about 200%-500%.

102. The method of claim 89, wherein the endogenous cellular gene is a selected from the group consisting of FAD2-1, EPO, GM-CSF, GDNF, VEGF, and LDL-R, and Her2/Neu.

103. The method of claim 89, wherein the endogenous cellular gene is VEGF.

104. The method of claim 89, wherein the activation of gene expression prevents repression of gene expression.

105. The method of claim 93 or 95, wherein the regulatory domain is selected from the group consisting of a transcriptional activator, or a histone acetyltransferase.

106. The method of claim 89, wherein the step of administering the nucleic acid molecule to the cell comprises administering the nucleic acid molecule in a lipid:nucleic acid complex or as naked nucleic acid.

107. The method of claim 89, wherein the nucleic acid molecule is an expression vector comprising a zinc finger protein-encoding nucleic acid operably linked to a promoter.

108. The method of claim 107, wherein the expression vector is a viral expression vector.

109. The method of claim 108, wherein the expression vector is a retroviral expression vector, an adenoviral expression vector, or an AAV expression vector.

110. The method of claim 89, wherein the promoter is an inducible promoter.

111. The method of claim 89, wherein the promoter is a weak promoter.

112. The method of claim 89, wherein the cell comprises less than about 1.5×10^6 copies of the zinc finger protein.

113. The method of claim 89, wherein the target site is upstream of a transcription initiation site of the endogenous cellular gene.

114. The method of claim 89, wherein the target site is adjacent to a transcription initiation site of the endogenous cellular gene.